REMARKS

Claims 40, 41, 45, 46, 54, 55, 58-63, and 66-83 were pending prior to this Response. By the present communication, no claims have been added and claims 62, 63, 66-68, 80, and 81 have been cancelled without prejudice. In addition, claims 40, 45, 46, 58, 59, 69, 72, 74, 75, 76, 77, 78, 82 and 83 have been amended to define Applicant's invention with greater particularity and for the purpose of placing the claims in condition for allowance. The claim amendments would add no new matter, being fully supported by the Specification and original claims. Accordingly, upon entry of the amendments claims 40, 41, 45, 46, 54, 55, 58-61, and 69-79, 82, and 83 would be pending.

The Objection to the Claims

The Office Action indicates that claims 44 45, 46, 58, 66, 67, 71, 72, 74-77 and 81 are objected to as allegedly containing informalities. By the present communication, claims 66, 67 and 81 are cancelled, rendering moot the objection to claims 66 and 67 and 81. Claim 44 was previously cancelled. The remaining claims have been amended to overcome the objection as follows:

Claims 71 and 74-77 are objected to for allegedly being improperly dependent. To overcome the informality, claims 71 and 74-77 have been amended to correct dependency by placing dependency upon an earlier numbered pending claim.

Claims 45 and 58 are objected to for omission of "the" before "nucleic acid" in the phrase "operatively linked to nucleic acid at line 2 thereof. To overcome the informality, claims

45 and 58 have each been amended to insert the term "the" prior to "nucleic acid" in the phrase at issue.

Claims 46, 59, 72, and 76 are objected to for containing a Markush group wherein the last 6 elements of the group fail to include the term "promoters." To overcome the rejection, claims 46, 59, 72, and 76 have each been amended to insert the term "promoter" following the last six elements of the Markush group.

Claim 75 is objected to for omission of the term "linked" in the phrase "element operatively to the nucleic acid" at line 2. To overcome the objection, the term "linked" has been inserted following "operatively" in the phrase at issue.

In view of the above amendments, Applicant respectfully submits that all objections to the claims are now overcome and reconsideration and withdrawal of the objections to the claims are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 62, 63 and 66-68 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. By the present communication, claims 62, 63 and 66-68 are now cancelled, thus rendering the rejection moot. Accordingly, Applicant respectfully requests withdrawal of the rejection.

The Rejection under 35 U.S.C. § 103

A. Applicant respectfully traverses the rejection of claims 40, 41, 54, 55, 60-63, 68-70, 73, 74, 78 and 79 as allegedly lacking patentability over U. S. Patent No. 6,027,159 to Kaufman et al (hereinafter "Kaufman) in view of U.S. Patent No. 5,891,435 to Muir et al. (hereinafter "Muir).

Claims 62-68 are now cancelled, thus rendering the rejection moot as to the subject matter of these claims.

With regard to remaining claims 40, 41, 54, 55, 60-61, 69-70, 73, 74, 78 and 79, Applicant submits that the invention immunomodulating compositions for treating autoimmune diabetes, as defined by amended claims 40 and 69, distinguish over the combined disclosures of Kaufmann and Muir by requiring "one or more nucleic acid construct encoding GAD self-antigen (or insulin B-chain self antigen) and IL-10 (or selected from IL-10 and IL-4 and a combination thereof (claim 69)) in a pharmaceutically acceptable carrier." Moreover, Applicant submits that the invention methods for treating autoimmune diabetes in a subject in need thereof, as defined by amended claims 54 and 73, distinguish over the combined disclosures of Kaufman and Muir by requiring "administering to the subject by peripheral administration an immunomodulatory effective amount of one or more nucleic acid constructs encoding GAD self-antigen and IL-10 or insulin B-chain and IL-10 or IL-4, in a pharmaceutically acceptable carrier, wherein transient expression in the subject treats the autoimmune diabetes.

Kaufmann fails to disclose a composition comprising one or more nucleic acid constructs encoding GAD self-antigen and IL-10 in a pharmaceutically acceptable carrier or encoding insulin B-chain and IL-10 and or IL-4. Instead of describing the invention compositions, as asserted by the Examiner, Kaufmann describes the in vivo presence of GAD65 self antigen in individuals undergoing autoimmune response (Col 3, lines 1-10 and 46-55) or a "pancreatic B-cell associated antigen" (i.e., a *protein*, such as GAD65 or insulin B-chain) administered alone or in combination with "an adjuvant" (Col. 4, lines 27-36). IL-4 and IL-10 are included in the list of "adjuvants" along with "immunogenic" mRNA and DNA, but Kaufmann provides no suggestion that nucleic acids contained in a vector that encode the antigen *and* the cytokine IL-10 and/or IL-4 could be substituted for protein antigens and cytokines because Kaufmann's

disclosure is limited to inducing immune response using protein antigen that is either "purified" or "synthesized by standard fluoroenyl methoyloxycarbonyl (fmoc) chemistry and purified by chromatography" (Col. 10, lines 37-44).

The Examiner relies upon Muir as disclosing compositions for treating a condition of autoimmune process comprising "one or more nucleic acid constructs (viral vectors), for example at Col. 5, lines 29-52 and in Example 4 (Office Action, page 5). However, Muir is absolutely silent regarding a composition containing "one or more nucleic acid constructs encoding GAD self-antigen *and* IL-10 or insulin B-chain *and* IL-10 or IL-4, or a combination thereof, in a pharmaceutically acceptable carrier that is effective for treating autoimmune diabetes. Even in Example 4, where Muir discloses using live virus as a vector there is no hint that either IL-10 or IL-4 could or should be included in a vaccine for delivering nucleic acid encoding self-antigen. In fact, in Example 4, Muir is absolutely silent regarding administration of self-antigen in conjunction with IL-10 or IL-4 in a vaccine, whether a protein vaccine or a nucleic acid vector vaccine.

The only referral to either cytokine in Muir is in relation to autorelease of "inhibitory cytokines (e.g., interleukin-10 . . . " in mice immunized with the B chain of insulin (Col. 7, line 59) or use of IL-10 in conjunction with GAD65 for delaying onset of diabetes (Col. 9, lines 29-48). There is no suggestion in Muir that pathogenesis of autoimmune diabetes can be permanently delayed or that the combination can be used in treatment of autoimmune diabetes once established.

Thus, Applicant respectfully submits that neither Kaufman nor Muir, nor the combined disclosures of the two, are sufficient to suggest the invention compositions and methods of treating autoimmune diabetes.

Moreover, even if those of skill in the art would have been motivated to combine the disclosures of Kaufman and Muir in the way asserted by the Examiner, there would have been no reasonable expectation on the part of those skilled in the art that adding nucleic acid encoding IL-10 to a vector containing nucleic acid encoding GAD65 or adding nucleic acid encoding IL-10 and/or IL-4 to a vector containing nucleic acid encoding insulin B chain would result in a composition effective for treatment of autoimmune diabetes because, rather than adding DNA encoding any cytokine to the vaccine. Muir recommends as an adjuvant to a viral vector-containing composition "a non-specific irritant to attract leukocytes or enhance an immune response," including such substances as mineral oil, water, aluminum hydroxide, and the like (Example 4).

Accordingly, Applicant respectfully submits that *prima facie* obviousness of present claims 40, 41, 54, 55, 60-61, 69-70, 73, 74, 78 and 79 is not established over Kaufman in view of Muir, and reconsideration and withdrawal of the rejection are respectfully requested.

B. Applicant respectfully traverses the rejection of claims 40, 41, 45, 46, 54, 55, 58-63, and 66-82 as allegedly being unpatentable under 35 U.S.C. § 103 over Kaufman and Muir as applied above and further in view of U.S. Patent No. 6,313,272 to Greve et al. (hereinafter "Greve"). Claims 62, 63, 66, 67, 80 and 81 are now cancelled without prejudice, rendering the rejection moot as to the subject matter of these claims.

Applicant submits that the invention immunomodulating compositions for treatment of autoimmune diabetes, as defined by amended claim 40, distinguish over the combined disclosures of Kaufmann, Muir, and Greve by requiring "one or more nucleic acid constructs encoding GAD self-antigen and IL-10 in a pharmaceutically acceptable carrier" and the invention methods for treating autoimmune diabetes, as defined by claim amended claim 54,

distinguish over the cited art by requiring "administering to the subject by peripheral administration an immunomodulatory effective amount of one or more nucleic acid construct encoding GAD self-antigen and IL-10 in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the IL-10 in the subject treats the autoimmune diabetes. "

Regarding the remaining rejected claims, the remarks above concerning the insufficiency of the combined disclosures of Kaufman and Muir for disclosing or suggesting the invention compositions and methods under 35 U.S.C. § 103 apply equally and are incorporated here with respect to pending claims 40, 41, 45, 46, 54, 55, 58.

In addition, Applicant submits that Greve does not cure these deficiencies in the disclosure of Kaufman and Muir. The Examiner relies upon Greve as disclosing advantageous use of nucleic acid constructs operably linked to various promoters to regulate the expression of IL –4 in a method of treating autoimmune diabetes" , especially at Col. 2, lines 35-53 and Col 6, lines 36-54. (Office Action, page 7). However, at Col 2, lines 35-53, Greve actually discloses use of nucleic acid encoding a *mutant* IL-4 that is *an agonist* of naturally secreted IL-4. Greve does not disclose a nucleic acid encoding the cytokine IL-4 in a therapeutic composition for treatment of autoimmune diabetes. Thus, Applicants submit that Greve does not overcome the deficiencies of Kaufman and Muir so that the combination of the three would suggest the invention compositions and methods to those of skill in the art.

In addition, Applicant submits that those of skill in the art would not be motivated by Greve's disclosure of an IL-4 mutant that binds to IL-4 receptors on T cells to arrive at the invention methods and compositions because such a mutant IL-4 does not act as a cytokine and does not have a direct therapeutic effect. Moreover, those of skill in the art would not have a reasonable expectation in view of the combined disclosures of Kaufman, Muir and Greve, that transient expression of IL-4 and a GAD self-antigen sufficient to treat autoimmune diabetes

could be accomplished by peripheral administration of nucleic acid encoding such polypeptides because Greve's disclosure does not pertain to raising an immune response in a subject to the mutant IL-4 disclosed therein.

C. Applicant respectfully traverses the rejection of claims 40, 41, 45, 46, 54, 55, 58-63, and 66-82 as allegedly being unpatentable under 35 U.S.C. § 103 over Kaufman, Muir, and Greve as applied above and further in view of U.S. Patent No. 5,951,976 to Segal et al. (hereinafter "Segal"). Claims 62, 63, 66, 67, 80 and 81 are now cancelled without prejudice, rendering the rejection moot as to the subject matter of these claims.

Applicant submits that the invention immunomodulating compositions for treatment of autoimmune diabetes, as defined by amended claim 40, distinguish over the combined disclosures of Kaufmann, Muir, Greve and Segal by requiring "one or more nucleic acid constructs encoding GAD self-antigen and IL-10 in a pharmaceutically acceptable carrier" and the invention methods for treating autoimmune diabetes, as defined by claim amended claim 54, distinguish over the cited art by requiring "administering to the subject by peripheral administration an immunomodulatory effective amount of one or more nucleic acid construct encoding GAD self-antigen and IL-10 in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the IL-10 in the subject treats the autoimmune diabetes. "

Regarding the remaining rejected claims, the remarks above concerning the insufficiency of the combined disclosures of Kaufman, Muir, and Greve for disclosing or suggesting the invention compositions and methods under 35 U.S.C. § 103 apply equally and are incorporated here with respect to pending claims 40, 41, 45, 46, 54, 55, 58.

In addition, Applicant submits that Segal does not cure these deficiencies in the disclosure of Kaufman, Muir, and Greve. The Examiner relies upon Segal as disclosing advantageous expression of naked nucleic acids which may encode a GAD self-antigen and

interleukins 4 and 10. However, the disclosure of Segal pertains to vaccines comprising *a cell* mixed with or expressing a recombinant opsonin, which is defined by Segal as a molecule which is contemporaneously bound or attached to both an antigen and an antigen-presenting cell so as to allow more efficient coupling and internalization of the antigen by the APC (Background). Segal's disclosure regarding naked DNA pertains to introduction of the naked DNA in vitro into a cell and does not disclose or suggest use of naked DNA itself as a vaccine or composition for introduction into a mammalian subject for transient expression in the subject. use of nucleic acid constructs operably linked to various promoters to regulate the expression of IL –10 in a method of treating autoimmune diabetes" , especially at Col. 2, lines 35-53 and Col 6, lines 36-54. (Office Action, page 7). However, at Col 2, lines 35-53, Greve actually discloses use of nucleic acid encoding a *mutant* IL-4 that is *an agonist* of naturally secreted IL-4. Greve does not disclose a nucleic acid encoding the cytokine IL-4 in a therapeutic composition for treatment of autoimmune diabetes. Thus, Applicants submit that Segal does not overcome the deficiencies of Kaufman, Muir and Greve so that the combination of the four references would suggest the invention compositions and methods to those of skill in the art.

In addition, Applicant submits that those of skill in the art would not be motivated by Segal's disclosure of a cell expressing an opsonin to arrive at the invention methods and compositions because Segal does not suggest that DNA encoding GAD65 and IL-4 could be used as a treatment of autoimmune diabetes without being incorporated into a cell for antigen presentation as a opsonin. Moreover, those of skill in the art would not have a reasonable expectation in view of the combined disclosures of Kaufman, Muir, Greve and Segal, that transient expression of IL-4 and a GAD self-antigen by the patient's own system would be sufficient to treat autoimmune diabetes or could be accomplished by peripheral administration of nucleic acid encoding such polypeptides because Segal's disclosure does not pertain to raising an

immune response in a subject by means of administering DNA in a vector or naked DNA encoding the antigen and the cytokine without the DNA being first inserted into a cell for expression.

Accordingly, Applicant respectfully submits that *prima facie* obviousness of invention methods and compositions as recited in claims 40, 41, 45, 46, 54, 55, 58 is not established over the combination of Kaufman, Muir, Greve, and Segal, and reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, it is believed that all objections and rejections are overcome. Therefore, Applicant respectfully requests entry of the amendments and passage of the claims to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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